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Research Article

Anti-Hyperglycemic Activity of Urtica dioica Extract in Obese Male Sprague Dawley Rats: Evaluation of HOMA-IR and HOMA-β

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ABSTRACT

Obesity is characterized by adipocyte accumulation that impairs glucose uptake, leading to insulin resistance, hyperglycemia, and an increased risk of diabetes mellitus. Given the limitations and adverse effects of pharmacological therapies for diabetes, alternative agents are needed. *Urtica dioica* contains flavonoids with anti-inflammatory and antioxidant properties that may improve glucose homeostasis. This experimental study employed a pre-test and post-test control group design using 25 male Sprague Dawley rats divided into five groups: healthy control (K1), obese control (K2), and three obese groups receiving *Urtica dioica* extract at doses of 125, 250, and 500 mg/kgBW (D1–D3) for four weeks. Data were analyzed using one-way ANOVA and a paired t-test. Administration of *Urtica dioica* extract at 500 mg/kgBW (D3) significantly reduced blood glucose (79.90 ± 2.51 vs. 177.92 ± 3.30; $p<0.05$), increased insulin levels (16.20 ± 0.29 vs. 12.82 ± 0.28; $p<0.05$), decreased HOMA-IR (3.19 ± 0.07 vs. 5.63 ± 0.14; $p<0.05$), and enhanced HOMA-β (351.20 ± 58.77 vs. 40.21 ± 1.63; $p<0.05$) compared with untreated obese controls. In conclusion, a 4-week administration of Urtica dioica extract effectively improved insulin resistance and β-cell function in obese rats, with the most pronounced effect observed at 500 mg/kgBW.

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INTRODUCTION

Obesity is a global health problem with an increasing prevalence; more than 1 billion people worldwide are obese, including 650 million adults, 340 million adolescents, and 39 million children (WHO, 2022). According to the 2023 Indonesian Health Survey, the prevalence of obesity among adults aged 18 years and older was 23.4%. The highest prevalence was observed in the 40–44-year age group, reaching 30.4% (RISKESDAS, 2023). The World Health Organization (WHO) defines obesity as abnormal or excessive fat accumulation that poses health risks, and it is one of the leading causes of mortality in both developed and developing countries (Lin & Li, 2021).

The pathogenesis of obesity is associated with an imbalance between energy intake and expenditure, leading to fat accumulation (Jin *et al*., 2023). This condition reduces tissue glucose uptake and induces adipose tissue dysfunction, resulting in excessive release of pro-inflammatory cytokines and free fatty acids (FFA) in adipose tissue, muscle, liver, and vascular endothelium, ultimately causing insulin resistance (Gołacki *et al*., 2022). Insulin resistance and pancreatic β-cell function can be assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and β-cell function (HOMA-β) (Khalili *et al*., 2023). These indices were chosen because they are widely validated, minimally invasive, cost-effective, and provide reliable estimates of insulin sensitivity and pancreatic β-cell activity based on fasting glucose and insulin levels (Krzymien & Ladyzynski, 2024).

Diabetes mellitus, a common consequence of obesity, can lead to microvascular and macrovascular complications, including retinopathy, nephropathy, heart failure, and central nervous system disorders (Ghalavand *et al*., 2017; Lu *et al*., 2024). Pharmacological therapies such as sulfonylureas, thiazolidinediones (TZDs), and biguanides are effective in lowering blood glucose levels but may cause side effects, including hypoglycemia, vitamin B12 deficiency, and lactic acidosis (Association, 2013; Chaudhury *et al*., 2017). Therefore, alternative treatments with fewer side effects are urgently needed.

Bioactive compounds from plants, particularly flavonoids, have been widely investigated as antidiabetic agents. Flavonoids are polyphenolic compounds found in vegetables, fruits, tea, cocoa, grains, and spices, with known anti-inflammatory and antioxidant properties (Al-Ishaq *et al*., 2019; Oteiza *et al*., 2021). Based on their classification, flavonoids include flavonols (quercetin, kaempferol, myricetin), flavanones (eriodictyol, hesperetin, naringenin), isoflavonoids (daidzein, genistein, glycitein), flavones (apigenin, luteolin), flavan-3-ols (catechin), and anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin). Flavonoids are recognized for their anti-obesity and antidiabetic potential (Kawser Hossain *et al*., 2016).

Stinging nettle (*Urtica dioica*), a member of the Urticaceae family, is widely found in Indonesia. This plant contains flavonoids, tannins, alkaloids, phenols, and saponins (Bhusal *et al*., 2022). Flavonoids in *U. dioica*, such as quercetin and ferulic acid, are known to stimulate insulin secretion and protect pancreatic β-cells (Dhanya, 2022; Salau *et al*., 2023). Their mechanisms include inhibiting intestinal glucose absorption, enhancing insulin receptor sensitivity, and reducing oxidative stress and inflammation (Aryaeian *et al*., 2017). Several studies have demonstrated that *U. dioica* extract lowers blood glucose levels, improves insulin sensitivity, and prevents β-cell

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damage in diabetic rat models (Ahangarpour *et al*., 2012; Gohari *et al*., 2018; Ranjbari *et al*., 2016).

However, previous studies have not comprehensively examined the effects of *U. dioica* extract derived from the entire plant (leaves, stems, and roots) on hyperglycemia induced by obesity. Obesity triggers FFA release, inflammation, and oxidative stress (reduced SOD and CAT activity), which impair tissue glucose uptake, induce insulin resistance, and eventually progress to diabetes. Therefore, this study aimed to evaluate the effects of *U. dioica* extract on HOMA-IR and HOMA-β in obese rats.

METHODS

Research Subjects

This study used 25 male Sprague Dawley rats aged 7–8 weeks with an average body weight of 180.16 ± 2.64 g. The research protocol was approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (No. KE/FK/1049/EC/2023). Identification of *Urtica dioica* was conducted at the Plant Systematics Laboratory, Faculty of Biology, Universitas Gadjah Mada (Reg. No. 0172/STb/XI/2022).

Extract Preparation

The parts of *U. dioica* used included leaves, stems, and roots. Samples were washed, chopped, and dried in a cabinet dryer at approximately 45 °C, then ground into powder. Extraction was performed by maceration using 70% ethanol for 3 × 24 hours, with solvent replacement every 24 hours. The macerates were collected and evaporated using a rotary evaporator to obtain a thick extract (Fadilah & Susanti, 2020).

Obesity Induction and Animal Treatment

The rats were acclimatized for seven days at the Inter-University Center (PAU) for Food and Nutrition, Universitas Gadjah Mada. Obesity was induced over six weeks through ad libitum administration of a high-fat and fructose diet (HFFD), along with 1% body weight fructose delivered daily via oral gavage. Following obesity induction, the rats were randomly allocated into five groups (n = 5 per group): K1 (healthy control), K2 (obese control), D1 (obese + *Urtica dioica* extract 125 mg/kgBW), D2 (obese + *Urtica dioica* extract 250 mg/kgBW), and D3 (obese + *Urtica dioica* extract 500 mg/kgBW).

The sample size (five rats per group) was determined based on Federer's formula:

$$(t-1)(r-1) \geq 15$$

Where *t* represents the number of experimental groups and *r* the number of replicates, ensuring an adequate residual degree of freedom for one-way ANOVA analysis while adhering to the ethical principle of minimal animal use. The extract intervention was administered orally via gavage for four weeks (Novianti, 2024).

Blood Sampling

Blood sampling was performed in the morning between 08:00 and 10:00 a.m. after an overnight fast (10–12 hours) via the retro-orbital plexus under light anesthesia. Blood samples were collected using microhematocrit tubes and centrifuged at 4,000 rpm for 15 minutes to obtain serum.

Blood Glucose Measurement

Blood glucose levels were measured using the enzymatic glucose oxidase-peroxidase aminophenazone (GOD-PAP) method with a UV-Vis spectrophotometer at 500 nm.

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Insulin Measurement

Insulin levels were analyzed using a commercial Enzyme-Linked Immunosorbent Assay (ELISA) kit (Fine Test) according to the manufacturer's protocol.

HOMA-IR Calculation

HOMA-IR was calculated using the following formula:

$$\text{HOMA-IR: } \frac{\text{Fasting Glucose } \left(\frac{\text{mg}}{\text{dL}}\right) \text{x Fasting Insulin } (\mu\text{IU/mL})}{405}$$

The constant 405 is derived from the original HOMA model by Matthews *et al*. (1985), which uses glucose expressed in mg/dL. It represents an approximate conversion factor from the standard formula using mmol/L:

$$\text{HOMA-IR: } \frac{\text{Fasting Glucose } \left(\frac{\text{mmol}}{\text{L}}\right) \text{x Fasting Insulin } (\mu\text{IU/mL})}{22.5}$$

Where 1 mmol/L of glucose equals 18 mg/dL ($22.5 \times 18 \approx 405$), this clarification ensures consistency in units and facilitates comparison with studies employing glucose values in mg/dL.

HOMA-β Calculation

HOMA-β was calculated using the following formula:

$$\text{HOMA-}\beta\text{: } \frac{360 \text{ x Fasting Insulin } (\mu\text{IU/mL})}{\text{Fasting Glucose } \left(\frac{\text{mg}}{\text{dL}}\right) - 63}$$

This formula is adapted from the original HOMA model proposed by Matthews *et al*. (1985), which describes the homeostatic relationship between fasting glucose and insulin levels. The constants 360 and 63 are derived from the original equation, expressed in glucose units (mmol/L; HOMA-β = [20 × Insulin]/[Glucose – 3.5]), and converted to mg/dL by multiplying by 18 (1 mmol/L = 18 mg/dL). These constants ensure consistency in units and allow comparison with studies that use glucose in mg/dL.

Data Analysis

Data on glucose, insulin, HOMA-IR, and HOMA-β were tested for normality using the Shapiro-Wilk test and for homogeneity using Levene's test. Differences between groups were analyzed using a one-way ANOVA, followed by the Least Significant Difference (LSD) post hoc test. Paired t-tests were applied to compare pre- and post-intervention results.

RESULTS

Blood Glucose Levels

Blood glucose levels were measured before (pre-test) and after (post-test) *Urtica dioica* extract intervention. Shapiro-Wilk normality and Levene's homogeneity tests confirmed that the data were normally distributed and homogeneous ($p > 0.05$). One-way ANOVA revealed significant differences among groups ($p = 0.000$).

Post-hoc LSD analysis showed that glucose levels in the healthy control group (K1) were significantly lower than those in the obese control group (K2) and all treatment groups at pre-test. After the intervention, glucose levels in D1, D2, and D3 decreased significantly compared to K2, with the greatest reduction observed in D3. Paired t-tests confirmed significant pre–post changes ($p = 0.000$) in all treatment groups, indicating that higher doses of the extract produced a greater glucose-lowering effect.

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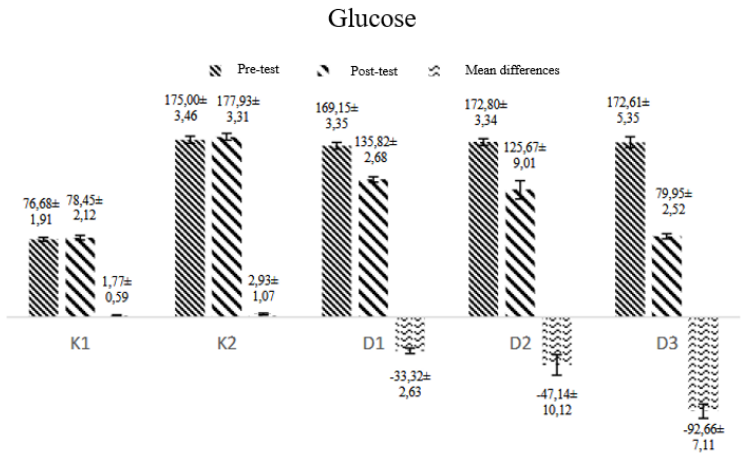

Figure 1. Changes in blood glucose levels before and after *Urtica dioica* extract intervention (mg/dL).

Blood Insulin Levels

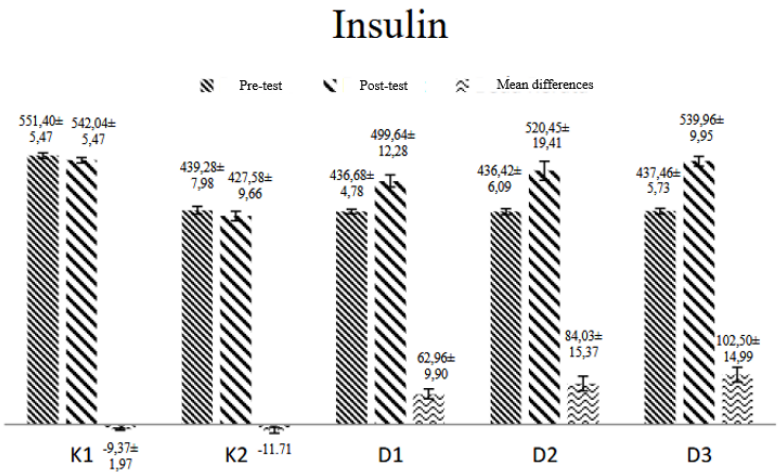

Figure 2. Changes in blood insulin levels before and after *Urtica dioica* extract intervention (µIU/mL).

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Insulin levels were also analyzed at pre-test and post-test. The data were normally distributed and homogeneous (p > 0.05). ANOVA demonstrated significant differences among groups (p = 0.000). Prio Obesity is characterized by adipocyte accumulation that impairs glucose uptake, leading to insulin resistance, hyperglycemia, and an increased risk of diabetes mellitus. Given the limitations and adverse effects of pharmacological therapies for diabetes, alternative agents are needed. *Urtica dioica* contains flavonoids with anti-inflammatory and antioxidant properties that may improve glucose homeostasis. This experimental study employed a pre-test and post-test control group design using 25 male Sprague Dawley rats divided into five groups: healthy control (K1), obese control (K2), and three obese groups receiving *Urtica dioica* extract at doses of 125, 250, and 500 mg/kgBW (D1–D3) for four weeks. Data were analyzed using one-way ANOVA and a paired t-test. Administration of *Urtica dioica* extract at 500 mg/kgBW (D3) significantly reduced blood glucose (79.90 ± 2.51 vs. 177.92 ± 3.30; p<0.05), increased insulin levels (16.20 ± 0.29 vs. 12.82 ± 0.28; p<0.05), decreased HOMA-IR (3.19 ± 0.07 vs. 5.63 ± 0.14; p<0.05), and enhanced HOMA-β (351.20 ± 58.77 vs. 40.21 ± 1.63; p<0.05) compared with untreated obese controls. In conclusion, a 4-week administration of Urtica dioica extract effectively improved insulin resistance and β-cell function in obese rats, with the most pronounced effect observed at 500 mg/kgBW.

r to intervention, insulin levels in the obese groups (K2, D1, D2, D3) were lower than those in K1. Following the intervention, insulin levels in D1, D2, and D3 increased significantly compared with K2, with the greatest increase observed in D3. Paired t-tests showed significant pre–post changes (p = 0.000), confirming that higher doses were associated with greater improvements in insulin levels.

HOMA-IR values were calculated from blood glucose and insulin concentrations. The data were normally distributed and homogeneous (p > 0.05). ANOVA revealed significant intergroup differences (p = 0.000). At pre-test, HOMA-IR values in obese groups (K2, D1, D2, D3) were higher than in K1. After intervention, HOMA-IR values in D1, D2, and D3 decreased significantly compared to K2, with the lowest values found in D3. Paired t-tests also showed significant pre–post changes (p = 0.000), confirming that *U. dioica* extract reduced insulin resistance in a dose-dependent manner.

HOMA-IR

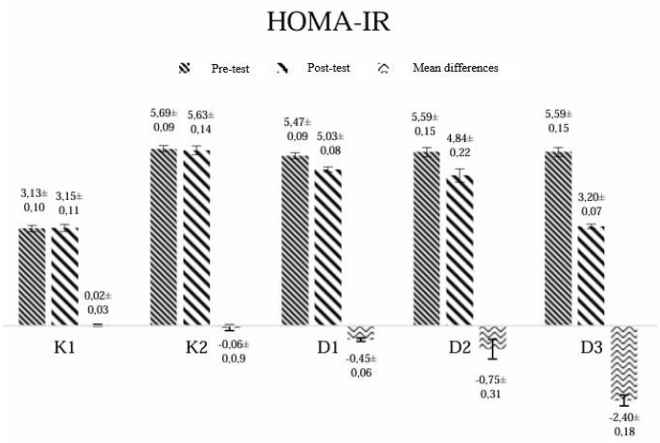

Figure 3. Changes in HOMA-IR before and after *Urtica dioica* extract intervention

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HOMA-β

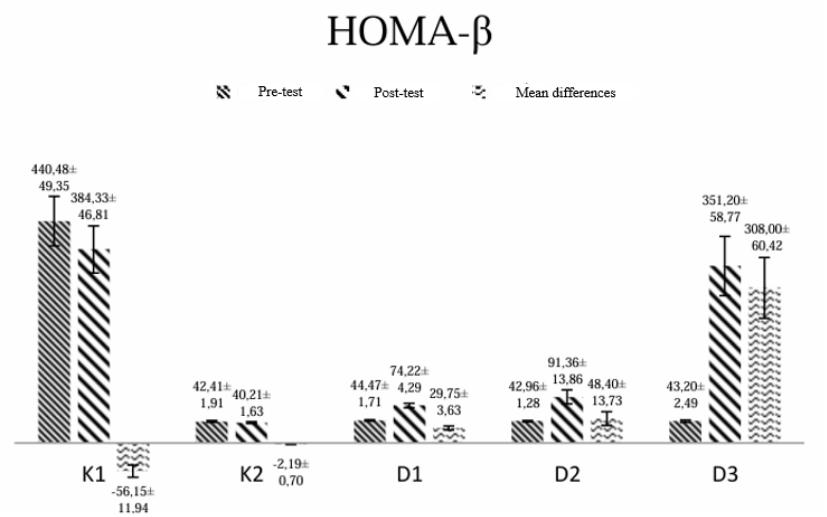

Figure 4. Changes in HOMA-β before and after *Urtica dioica* extract intervention

HOMA-β analysis showed normally distributed and homogeneous data ($p > 0.05$). ANOVA demonstrated significant differences among groups ($p = 0.000$). At pre-test, obese groups (K2, D1, D2, D3) had lower HOMA-β values compared to K1. Post-intervention, HOMA-β values increased significantly in D1, D2, and D3 compared with K2, with the greatest improvement observed in D3. Paired t-tests ($p = 0.000$) further confirmed that *U. dioica* extract effectively improved pancreatic β-cell function, particularly at the dose of 500 mg/kgBW.

DISCUSSION

The results of this study demonstrated that administration of *Urtica dioica* extract at various doses for four weeks significantly reduced blood glucose levels (paired t-test, p = 0.000). The most significant reduction was observed in group D3 (500 mg/kgBW), followed by D2 (250 mg/kgBW) and D1 (125 mg/kgBW), with all treatment groups showing better outcomes than the obese control group (K2). Furthermore, the one-way ANOVA followed by post-hoc LSD analysis revealed significant differences among the treatment groups (D1 vs D2, D1 vs D3, and D2 vs D3; p = 0.000), confirming the dose-dependent effect of *U. dioica* extract on glucose reduction. These findings are consistent with those of Ayoubi *et al.* (2013), who reported that *U. dioica* significantly lowered glucose levels by enhancing insulin secretion from pancreatic β-cells.

The glucose-lowering effect of *U. dioica* is thought to be associated with its polyphenol content, which can induce insulin secretion via activation of Adenosine Monophosphate-activated Protein Kinase (AMPK), enhance glucose uptake in muscle and adipose tissue, and inhibit hepatic glucose production (Golovinskaia & Wang, 2023). In addition, flavonoids in *U. dioica* can inhibit intestinal α-amylase and α-glucosidase, enzymes responsible for hydrolyzing carbohydrates into glucose (Barber *et al.*, 2021). Quercetin plays a role in reducing lipid peroxidation, inhibiting glucose absorption via GLUT2 in the intestine, suppressing Phosphatidylinositol

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3-kinase (PI3K) activity, and reducing hepatic gluconeogenesis and glycogenolysis (Al-Ishaq *et al*., 2019). These mechanisms also involve enhanced GLUT4 translocation to the plasma membrane via the AMPK pathway. Catechins can inhibit intestinal glucose absorption, while hesperidin and naringenin contribute to the regulation of PPARγ and GLUT4 expression in both the liver and adipose tissue (Shahwan *et al*., 2022).

In addition to lowering blood glucose, *U. dioica* extract also increased insulin levels. The highest increase was observed in group D3, followed by D2 and D1, whereas K2 had lower insulin levels. This indicates that *U. dioica* extract not only reduces glucose but also improves insulin secretion. Obanda *et al.* (2016) reported that *U. dioica* enhanced insulin sensitivity in skeletal muscle by counteracting the inhibitory effects of FFAs on Akt phosphorylation and insulin-induced glycogen synthesis.

Persistent hyperglycemia in obesity is strongly associated with increased production of Reactive Oxygen Species (ROS) (González *et al*., 2023). Excess ROS induces oxidative stress, impairing pancreatic β-cell function through endoplasmic reticulum (ER) stress(Wang & Wang, 2017). ER stress is triggered by Ca^{2+} depletion, accumulation of misfolded and unfolded proteins due to high glucose load, and exposure to pro-inflammatory cytokines. These conditions activate transcription factors such as C/EBP Homologous Protein (CHOP) and c-Jun N-terminal Kinase (JNK), upregulate pro-apoptotic proteins (Bcl-2), and downregulate anti-apoptotic proteins, contributing to β-cell apoptosis and decreased insulin production and secretion(Hanchang *et al*., 2019).

Administration of *Urtica dioica* extract also resulted in a significant reduction in HOMA-IR values (Figure 3). This finding is consistent with the report by Ranjbari *et al.* (2016), who evaluated the effects of *Urtica dioica* extract at various doses in diabetic animal models combined with exercise. However, the inclusion of exercise in their experimental design may have introduced a confounding factor, as physical activity itself enhances insulin sensitivity and glucose uptake through mechanisms independent of pharmacological intervention. Consequently, it becomes difficult to determine the extent to which the observed effects were attributable solely to the extract. In contrast, the present study excluded any exercise intervention, thereby providing a more isolated and accurate assessment of the intrinsic metabolic effects of *U. dioica* extract on insulin resistance and β-cell function. In this study, the low dose (125 mg/kgBW; D1) increased insulin secretion compared to the K2 group, whereas the medium dose (250 mg/kgBW; D2) demonstrated greater improvement in insulin resistance. The high dose (500 mg/kgBW; D3) exerted the most optimal effect in reducing insulin resistance, with HOMA-IR values approaching those of the normal group (K1).

Furthermore, *U. dioica* extract significantly improved HOMA-β, which reflects pancreatic β-cell function in insulin secretion (Ellerbrock *et al*., 2022). In this study, the most significant improvement was observed in D3 (Figure 4), confirming U. dioica's protective effect on β-cells. Gohari *et al.* (2018) also reported that *U. dioica* protects and supports β-cell regeneration. This protective mechanism is thought to be associated with hesperidin content, which enhances antioxidant activity (SOD and GPx), reduces Malondialdehyde (MDA) levels, and prevents β-cell apoptosis by upregulating anti-apoptotic Bcl-xL expression while downregulating pro-apoptotic Bax expression (Hanchang *et al*., 2019).

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Overall, these findings confirm that *Urtica dioica* extract at a dose of 500 mg/kgBW is the most effective in reducing blood glucose levels, increasing insulin secretion, improving insulin resistance (HOMA-IR), and enhancing pancreatic β-cell function (HOMA-β), compared with doses of 125 mg/kgBW and 250 mg/kgBW. Importantly, no observable signs of toxicity, abnormal behavior, or adverse effects were detected in rats administered the highest dose (500 mg/kgBW) throughout the intervention period, suggesting that this dosage was well tolerated. Nonetheless, this study has several limitations. The relatively small sample size may limit the statistical power and generalizability of the results. Additionally, parameters related to oxidative stress and inflammatory cytokines were not assessed, which could have provided further insight into the mechanisms underlying the observed metabolic improvements. Future studies with larger sample sizes, longer intervention durations, and broader biomarker analyses are warranted to confirm and extend these findings.

CONCLUSION

Administration of *Urtica dioica* extract in obese Sprague Dawley rats demonstrated significant antihyperglycemic effects. Interventions with doses of 125 mg/kgBW, 250 mg/kgBW, and 500 mg/kgBW effectively reduced blood glucose levels, increased insulin concentrations, improved insulin resistance (HOMA-IR), and enhanced pancreatic β-cell function (HOMA-β). The optimal effect was observed at a dose of 500 mg/kg BW.

REFERENCES

Ahangarpour, A., Mohammadian, M., & Dianat, M. (2012). Antidiabetic effect of hydroalcholic urtica dioica leaf extract in male rats with fructose-induced insulin resistance. *Iranian Journal of Medical Sciences*, *37*(3), 181–186.

Al-Ishaq, R. K., Abotaleb, M., Kubatka, P., Kajo, K., & Büsselberg, D. (2019). Flavonoids and Their Anti-Diabetic Effects: Cellular Mechanisms and Effects to Improve Blood Sugar Levels. *Biomolecules*, *9*(9). https://doi.org/10.3390/biom9090430

Aryaeian, N., Sedehi, S. K., & Arablou, T. (2017). Polyphenols and their effects on diabetes management: A review. *Medical Journal of the Islamic Republic of Iran*, *31*, 134. https://doi.org/10.14196/mjiri.31.134

Association, A. D. (2013). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*, *37*(Supplement_1), S81–S90. https://doi.org/10.2337/dc14-S081

Ayoubi, A., Omidi, A., Valizade, R., & Mousaei, A. (2013). Effect of hydroalcoholic extract of Aloe vera and Teucrium on serum glucose and lipid profile in streptozotocin diabetic male rats TT - رثا هسیاقم اروهئولآ نااهایگ یلکلاوردیه مراصع (Aloe barbadensis) و هرویلک (Teucrium polium)، رب حوطس یمرس و زکولگ فورپ. *Journals of Birjand University of Medical Sciences*, *20*(2), 144–152. http://journal.bums.ac.ir/article-1-1335-en.html

Barber, E., Houghton, M. J., & Williamson, G. (2021). Flavonoids as Human Intestinal α-Glucosidase Inhibitors. *Foods (Basel, Switzerland)*, *10*(8). https://doi.org/10.3390/foods10081939

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Jurnal Kedokteran
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http://journal.um-surabaya.ac.id/index.php/qanunmedika

Bhusal, K. K., Magar, S. K., Thapa, R., Lamsal, A., Bhandari, S., Maharjan, R., Shrestha, S., & Shrestha, J. (2022). Nutritional and pharmacological importance of stinging nettle (Urtica dioica L.): A review. *Heliyon*, *8*(6), e09717. https://doi.org/10.1016/j.heliyon.2022.e09717

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., Marco, A., Shekhawat, N. S., Montales, M. T., Kuriakose, K., Sasapu, A., Beebe, A., Patil, N., Musham, C. K., Lohani, G. P., & Mirza, W. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Frontiers in Endocrinology*, *8*, 6. https://doi.org/10.3389/fendo.2017.00006

Dhanya, R. (2022). Quercetin for managing type 2 diabetes and its complications, an insight into multitarget therapy. *Biomedicine & Pharmacotherapy*, *146*, 112560. https://doi.org/https://doi.org/10.1016/j.biopha.2021.112560

Ellerbrock, J., Spaanderman, B., Drongelen, J. van, Mulder, E., Lopes van Balen, V., Schiffer, V., Jorissen, L., Alers, R.-J., Leenen, J., Ghossein-Doha, C., & Spaanderman, M. (2022). Role of Beta Cell Function and Insulin Resistance in the Development of Gestational Diabetes Mellitus. *Nutrients*, *14*(12). https://doi.org/10.3390/nu14122444

Fadilah, N. N., & Susanti. (2020). Aktivitas Antihiperurisemia Ekstrak Tanaman Jelatang (Urtica dioca L.) pada Mencit. *HIJP : HEALTH INFORMATION JURNAL PENELITIAN*, *12*.

Ghalavand, A., Motamedi, P., Delaramnasab, M., & Khodadoust, M. (2017). The Effect of Interval Training and Nettle Supplement on Glycemic Control and Blood Pressure in Men WithType 2 Diabetes. *International Journal of Basic Science in Medicine*, *2*, 33–40. https://doi.org/10.15171/ijbsm.2017.08

Gohari, A., Noorafshan, A., Akmali, M., Zamani-Garmsiri, F., & Seghatoleslam, A. (2018). Urtica Dioica Distillate Regenerates Pancreatic Beta Cells in Streptozotocin-Induced Diabetic Rats. *Iranian Journal of Medical Sciences*, *43*(2), 174–183.

Gołacki, J., Matuszek, M., & Matyjaszek-Matuszek, B. (2022). Link between Insulin Resistance and Obesity-From Diagnosis to Treatment. *Diagnostics (Basel, Switzerland)*, *12*(7). https://doi.org/10.3390/diagnostics12071681

Golovinskaia, O., & Wang, C.-K. (2023). The hypoglycemic potential of phenolics from functional foods and their mechanisms. *Food Science and Human Wellness*, *12*(4), 986–1007. https://doi.org/https://doi.org/10.1016/j.fshw.2022.10.020

González, P., Lozano, P., Ros, G., & Solano, F. (2023). Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections. *International Journal of Molecular Sciences*, *24*(11). https://doi.org/10.3390/ijms24119352

Hanchang, W., Khamchan, A., Wongmanee, N., & Seedadee, C. (2019). Hesperidin ameliorates pancreatic β-cell dysfunction and apoptosis in streptozotocin-induced diabetic rat model. *Life Sciences*, *235*, 116858. https://doi.org/10.1016/j.lfs.2019.116858

Jin, X., Qiu, T., Li, L., Yu, R., Chen, X., Li, C., Proud, C. G., & Jiang, T. (2023). Pathophysiology of obesity and its associated diseases. *Acta Pharmaceutica*

QANUN MEDIKA
Jurnal Kedokteran
Fakultas Kedokteran FKUM Surabaya
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Sinica B, *13*(6), 2403–2424. https://doi.org/10.1016/j.apsb.2023.01.012

Kawser Hossain, M., Abdal Dayem, A., Han, J., Yin, Y., Kim, K., Kumar Saha, S., Yang, G.-M., Choi, H. Y., & Cho, S.-G. (2016). Molecular Mechanisms of the Anti-Obesity and Anti-Diabetic Properties of Flavonoids. *International Journal of Molecular Sciences*, *17*(4), 569. https://doi.org/10.3390/ijms17040569

Khalili, D., Khayamzadeh, M., Kohansal, K., Ahanchi, N. S., Hasheminia, M., Hadaegh, F., Tohidi, M., Azizi, F., & Habibi-Moeini, A. S. (2023). Are HOMA-IR and HOMA-B good predictors for diabetes and pre-diabetes subtypes? *BMC Endocrine Disorders*, *23*(1), 39. https://doi.org/10.1186/s12902-023-01291-9

Krzymien, J., & Ladyzynski, P. (2024). Insulin resistance: Risk factors, diagnostic approaches and mathematical models for clinical practice, epidemiological studies, and beyond. *Biocybernetics and Biomedical Engineering*, *44*(1), 55–67. https://doi.org/https://doi.org/10.1016/j.bbe.2023.12.004

Lin, X., & Li, H. (2021). Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Frontiers in Endocrinology*, *12*(September), 1–9. https://doi.org/10.3389/fendo.2021.706978

Lu, X., Xie, Q., Pan, X., Zhang, R., Zhang, X., Peng, G., Zhang, Y., Shen, S., & Tong, N. (2024). Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. *Signal Transduction and Targeted Therapy*, *9*(1), 262. https://doi.org/10.1038/s41392-024-01951-9

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*(7), 412–419. https://doi.org/10.1007/BF00280883

Novianti, A. D. A. D. A. P. S. M. D. (2024). *Desain Percobaan: Teori dan Aplikasi 0*.

Obanda, D. N., Ribnicky, D., Yu, Y., Stephens, J., & Cefalu, W. T. (2016). An extract of Urtica dioica L. mitigates obesity induced insulin resistance in mice skeletal muscle via protein phosphatase 2A (PP2A). *Scientific Reports*, *6*(February), 1–9. https://doi.org/10.1038/srep22222

Oteiza, P. I., Fraga, C. G., & Galleano, M. (2021). Linking biomarkers of oxidative stress and disease with flavonoid consumption: From experimental models to humans. *Redox Biology*, *42*, 101914. https://doi.org/10.1016/j.redox.2021.101914

Ranjbari, A., Azarbayjani, M. A., Yusof, A., Halim Mokhtar, A., Akbarzadeh, S., Ibrahim, M. Y., Tarverdizadeh, B., Farzadinia, P., Hajiaghaee, R., & Dehghan, F. (2016). In vivo and in vitro evaluation of the effects of Urtica dioica and swimming activity on diabetic factors and pancreatic beta cells. *BMC Complementary and Alternative Medicine*, *16*, 101. https://doi.org/10.1186/s12906-016-1064-6

RISKESDAS. (2023). Survei Kesehatan Indonesia 2023 (SKI). *Kemenkes*, 235.

Salau, V. F., Erukainure, O. L., Olofinsan, K. O., Bharuth, V., Ijomone, O. M., & Islam, M. S. (2023). Ferulic acid improves glucose homeostasis by modulation of key diabetogenic activities and restoration of pancreatic architecture in diabetic rats. *Fundamental & Clinical Pharmacology*, *37*(2), 324–339. https://doi.org/https://doi.org/10.1111/fcp.12860

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Jurnal Kedokteran
Fakultas Kedokteran FKUM Surabaya
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Shahwan, M., Alhumaydhi, F., Ashraf, G. M., Hasan, P. M. Z., & Shamsi, A. (2022). Role of polyphenols in combating Type 2 Diabetes and insulin resistance. *International Journal of Biological Macromolecules*, *206*, 567–579. https://doi.org/10.1016/j.ijbiomac.2022.03.004

Wang, J., & Wang, H. (2017). Oxidative Stress in Pancreatic Beta Cell Regeneration. *Oxidative Medicine and Cellular Longevity*, *2017*, 1930261. https://doi.org/10.1155/2017/1930261

WHO. (2022). *World Obesity Day 2022 – Accelerating action to stop obesity* (Issue February 2024, pp. 1–23).